GAUCHER'S DISEASE: CLINICAL FEATURES AND INDICATIONS FOR SPLENECTOMY

Report of 5 Cases

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GAUCHER'S disease is a rare familial disease characterized by the accumulation of the cerebroside, kerasin, in the cells of the reticuloendothelial system. It is classified with Niemann-Pick's and Hand-Schüller-Christian's diseases as a disorder of lipoid storage. The conspicuous clinical feature is extreme splenomegaly with minimal constitutional symptoms, and the diagnosis is established by finding the characteristic Gaucher's cells in the marrow aspirate. Since these cells may be easily overlooked, the marrow examination must be carefully conducted with cognizance of the possibility of their existence. The purpose of this presentation is to describe the clinical features in five cases, selected for their illustrative value, and to discuss the indications for splenectomy.

CASE REPORTS

Case 1. A seven year old Jewish girl was referred to the Clinic in November 1949 because of splenomegaly and hepatomegaly observed during a routine examination one year previously. The child had been a full-term infant and had had the usual childhood diseases. The parents and two siblings were healthy. Extensive studies including marrow aspiration had been performed in 1948, and the results had been reported to be normal with the exception of a mild anemia.

Physical examination on admission disclosed an alert and active child with minimal physical retardation. There was no significant pallor. The spleen was firm and descended to the umbilicus. The liver was 2 cm. below the costal margin. Peripheral lymphadenopathy was absent.

The hemoglobin content of the blood was 13 Gm. per 100 cc. (Haden-Hauser). The erythrocyte count was 4,790,000 per cu. mm. The hematocrit value was 43 cc. per 100 cc. of blood. The leukocyte count was 12,150 per cu. mm. with a normal differential count. The reticulocytes were 1.9 per cent and the icterus index was 4 units. The hypotonic saline fragility was normal. The Wright-stained films showed minimal hypochromia and poikilocytosis. The remainder of the clinical studies including liver function tests and x-ray studies of the gastrointestinal tract were normal. The parents were reluctant to have further marrow aspirations, so the marrow films made one year previously were reviewed and found to be normal.

A provisional diagnosis of Banti's syndrome was made in 1949 and the child was observed at regular intervals. In September 1951, many Gaucher's cells were found in

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a marrow specimen aspirated from the crest of the ilium. A follow-up examination in October 1953 revealed no significant change in the size of the spleen or in the blood counts.

Discussion. The presence of a large, firm spleen associated with hepatomegaly of at least one year's duration in an otherwise healthy Jewish child should suggest the possibility of Gaucher's disease. Banti's syndrome might be considered but such a diagnosis should not be accepted in the absence of other evidence of portal hypertension.

Case 2. A 35 year old Jewish woman had been aware of a large spleen since the age of 18 years when it was detected during her first pregnancy. When first admitted to the Clinic in 1935, the patient had no symptoms except periodic episodes of left upper abdominal pain. The physical examination disclosed mild pallor and a firm spleen extending to the iliac crest. The liver was also firm and extended 5 cm. below the costal margin. The hemoglobin content of the blood was 8.5 Gm. per 100 cc. The erythrocyte count was 3,290,000 per cu. mm. and the hematocrit value was 29 cc. The leukocyte count was 2500 per cu. mm. with a normal differential count. The blood films revealed a moderate decrease of platelets. The reticulocytes were 2.6 per cent and the icterus index was 3 units. A report on this patient had been published by Anderson[1] who had established the diagnosis of Gaucher's disease by splenic aspiration in 1932. One sister of the patient had died at the age of six years with an "enlarged abdomen," another sister had had a splenectomy at the age of seven for Gaucher's disease, and a third sister, 23 years of age, had an "enlarged spleen."

Discussion. It is of interest that the diagnosis in this patient was proved by splenic aspiration in 1932. This procedure was rarely employed at that time but is now generally accepted as a relatively safe procedure in selected patients. Bone marrow aspiration was introduced as a clinical test in 1927[2] but was not in general use in 1932. Today, marrow aspiration is preferred to splenic aspiration to confirm the diagnosis.

The familial occurrence of Gaucher's disease has been reported several times but no specific genetic pattern has been established.

Case 3. A 61 year old Jewish man was first found to have an enlarged spleen during a routine health examination in May 1943. There had been occasional upper abdominal distress which he attributed to daily calisthenics. The physical examination was normal except for the presence of a firm spleen extending 6 cm. below the costal margin, and a palpable liver. The hemoglobin content of the blood was 15 Gm. per 100 cc. The erythrocyte count was 5,340,000 per cu. mm. and the hematocrit value 45 cc. per 100 cc. The leukocyte count was 4350 per cu. mm. with a normal differential count. The icterus index was 6 units. Liver function studies and roentgen examination of the gastrointestinal tract were normal.

The patient was examined again in 1946, at which time the spleen was noted to have enlarged further. The results of hematologic studies including hypotonic saline fragility were within the range of normal and similar to the initial findings three years before. A sternal marrow aspiration was reported as cellular and nondiagnostic. In addition, complete blood studies of the patient's only child were normal.

Progress study in September 1950, seven years after the initial examination, revealed no significant change in the blood count. The spleen now reached the iliac crest. The sternal marrow aspiration was repeated, and a few typical Gaucher's cells were discovered.

In June 1952 the hemogram revealed a hemoglobin value of 11.6 Gm. per 100 cc. The erythrocyte count was 3,960,000 per cu. mm., and the hematocrit reading was 41 cc. The leukocyte count was 2350 per cu. mm. with a normal differential count. The icterus

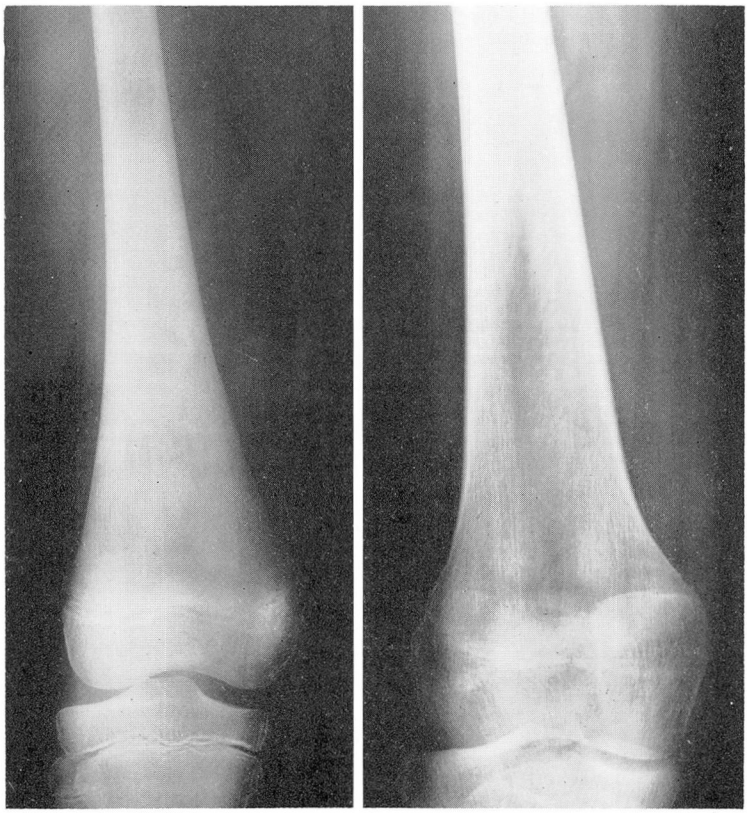
index was 15 units, and the reticulocytes were 4.1 per cent. The platelet count was 60,000 per cu. mm. Bleeding and coagulation times were normal though clot retraction was poor.

The most recent examination in October 1953 disclosed no significant clinical symptoms or change in the hematologic findings.

Discussion. This case illustrates the onset of clinical manifestations of the disease after mid-life. An experienced hematologist failed to recognize Gaucher's cells in the marrow films obtained in 1946. A review of these films, four years later, disclosed the presence of typical cells. This report illustrates how easily the specific Gaucher's cells may be overlooked unless the possibility of their existence is considered and the examination is conducted with extreme care.

It is possible that splenectomy would correct the pancytopenia in this case, but the mild clinical symptoms and the age of the patient make it unwise to advise surgery.

Case 4. A Jewish boy, nine years of age, was first observed in 1950. Splenectomy had been performed in 1947 because of a hemorrhagic diathesis due to thrombocytopenia associated with Gaucher's disease. The operation favorably influenced the hemor-



(a) (b)

Fig. 1. (a) (Case 4) "Erlenmeyer flask" appearance of distal femur in patient having Gaucher's disease. (b) Normal femur for comparison.

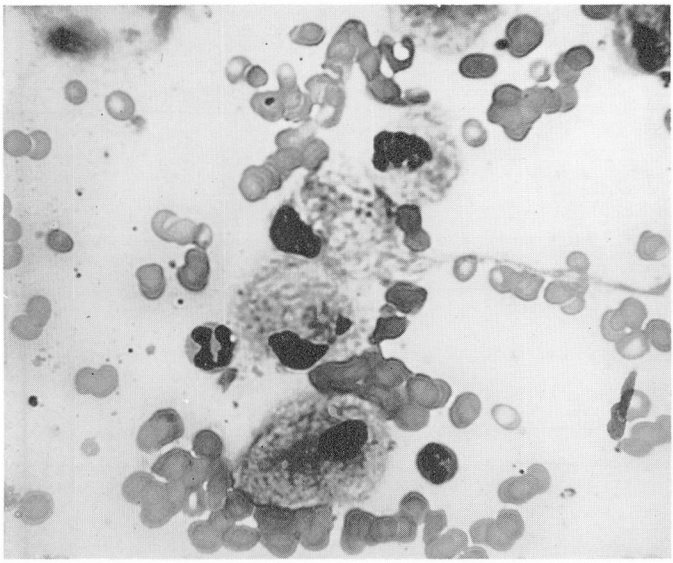


Fig. 2. (Case 5) Gaucher's cells from sternal marrow. Note large size of the cells and "wrinkled tissue paper" appearance of the cytoplasm. X600.

rhagic state. Dental extractions performed in 1950 were not followed by excessive bleeding. At that time the hemoglobin content of the blood was 11.8 Gm. per 100 cc. The erythrocyte count was 4,140,000 per cu. mm., and the hematocrit value 41 cc. per 100 cc. The leukocyte count was 17,200 per cu. mm. with 33 per cent neutrophilic granulocytes and 67 per cent lymphocytes. The bleeding and coagulation times were normal. X-ray studies of the bone disclosed typical changes observed in Gaucher's disease (fig. 1). In October 1952 the patient was asymptomatic and the examination revealed no significant change.

Discussion. It is apparent that in this patient splenectomy was beneficial in correcting the severity of the hemorrhagic diathesis due to the thrombocytopenia. The slight anemia that persisted may be the result of the marrow replacement by the Gaucher's cells. The osseous lesions demonstrated by roentgenographic examination caused no subjective symptoms. Bone pain and occasionally pathologic fractures may result from infiltration of the bone by the Gaucher's cells.

Case 5. A 39 year old Italian man was referred to the Clinic in July 1953 because of an enlarged spleen first observed during a routine insurance examination several months previously. Diagnostic examinations in his local hospital had failed to establish the cause of the splenic enlargement. The family history was noncontributory. The patient repeatedly stressed the fact that he was feeling well. He participated in active combat duty during World War II without difficulty.

Physical examination revealed an afebrile, well-nourished man. The liver edge was firm and palpable 5 cm. below the costal margin. The spleen was extremely firm and extended 5 cm. below the umbilicus. A sternal marrow aspiration revealed the presence of many typical Gaucher's cells (fig. 2). The hemoglobin content of the blood was 12.0 Gm. per 100 cc. The erythrocyte count was 4,500,000 per cu. mm. The hematocrit value was 41. The leukocyte count was 2600 per cu. mm. with a normal differ-

ential count. The reticulocytes were 3.3 per cent and the icterus index was 9 units. The erythrocytes showed moderate poikilocytosis and anisocytosis. The platelet count was moderately decreased. Roentgen studies disclosed bone lesions in the proximal femurs (fig. 3).

Discussion. The diagnosis of Gaucher's disease was suggested in this case by the benign nature of the marked splenomegaly and was easily established by marrow examination. The possibility of hereditary leptocytosis (Mediterranean anemia) was considered though the spleen was much larger than that usually observed in this condition. If the characteristic Gaucher's cells are scarce, their presence may be overlooked. We wish to emphasize the importance of alerting the hematologist who reviews the marrow films to the possibility of Gaucher's disease so that he will make a careful study of the thicker portion of the films.

There was no indication for recommending splenectomy.

COMMENT

Two clinical pictures of Gaucher's disease have been described. Oberling's[3] infantile type is manifested by a fulminating course with central nervous system involvement. The adult type is characterized by a prolonged chronic course. The disease was formerly believed to occur almost entirely in young persons, but it is now widely recognized that the condition often appears in later life. In Reich's[4] series of 20 patients, 10 were over 40 years of age. Reports[5] have stressed the familial incidence of the disease but no definite genetic pattern of transmission has been established. The disease has been observed in many races, but it most frequently occurs in Jewish people.

The clinical manifestations of the disease are due to the presence of kerasin-filled reticuloendothelial cells in various organs and vary with the degree of infiltration of the organs. The spleen, liver, bone marrow, lymph nodes, kidneys, eyes, central nervous system and other tissues may show infiltration by Gaucher's cells.[6-12]

The cases presented in this report illustrate that the disease may become evident at any age, progress slowly and often cause minimal systemic symptoms. The outstanding feature of the disease is the splenomegaly. In three of the five patients the chance observation of an enlarged spleen eventually led to the correct diagnosis. There are few diseases in a nontropical climate which present splenic enlargement of the degree observed in Gaucher's disease. It is not uncommon for the spleen to descend below the pelvic brim. For clinical purposes the presence of a huge firm spleen should lead the physician to consider Gaucher's disease, myeloid metaplasia of the spleen, chronic leukemia and malignant lymphoma. The liver is also enlarged in Gaucher's disease but to a lesser degree than is the spleen. Skeletal changes due to infiltration with Gaucher's cells are frequently detected on roentgenograms. Though the disease is usually asymptomatic, bone pain does occur and occasionally pathologic fractures are noted.[13] The long bones and those of the pelvis, spine, and skull are most commonly involved.[14] The "Erlenmeyer flask" appearance of the distal femur is considered to be characteristic of Gaucher's disease (fig. 1).

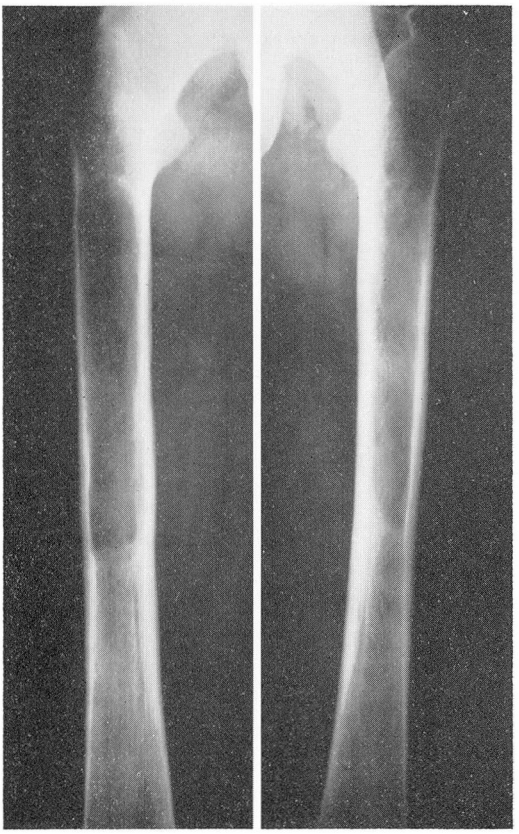


Fig. 3. (Case 5) Bone lesions of femurs in patient having Gaucher's disease.

The patients often show a mild to moderate, normocytic, normochromic anemia depending upon the severity and duration of the disease. Leukopenia is common and is due to granulocytopenia. Thrombocytopenia is frequently observed and may be sufficiently severe to cause purpura, epistaxis, and gingival bleeding. In certain patients the presence of reticulocytosis and the increase of serum bilirubin suggest that the anemia is due in part to excessive hemolysis of erythrocytes. The erythrocyte fragility in hypotonic saline is not altered.

The mechanism of the hematologic changes has not been established. In some patients the infiltration of the marrow by Gaucher's cells may explain the depression of the erythrocytes, granulocytes and thrombocytes. In other patients pancytopenia has been observed in the presence of a hypercellular marrow with minimal infiltration by Gaucher's cells, suggesting that "secondary hypersplenism" plays a major role. It has been recognized for many years

that marked splenomegaly resulting from various diseases may cause a depression of the cellular elements of the peripheral blood.[15]

Although opinions differ as to the indications for splenectomy in Gaucher's disease, there is general agreement that the operation is justified in patients who are experiencing distressing symptoms due to the increased size of the organ. Splenectomy is not warranted as a preventative measure to avoid spontaneous or traumatic rupture, since only one case of traumatic rupture of the spleen in Gaucher's disease has been recorded.[16] There is convincing evidence that splenectomy is beneficial in patients with pancytopenia and a hypercellular marrow if clinical manifestations, such as hemorrhagic diathesis and hemolytic anemia, are present. The mere demonstration of a "secondary hypersplenism" of mild degree by hematologic study does not justify splenectomy. When patients do not obtain clinical or hematologic benefit from splenectomy,[17] the failure to improve is presumably due to irreversible and marked marrow replacement due to Gaucher's cells rather than to hypersplenic effects. Splenectomy does not arrest the progression of the disease because progression of pancytopenia and bone changes have been observed after splenectomy.[10,17,18] Logan[18] cited several instances of patients who survived more than 15 years after splenectomy and included one patient who lived for 31 years after surgery. This report does not prove, however, that splenectomy increases the life span of patients with Gaucher's disease.

SUMMARY

Five reports of patients with Gaucher's disease are presented to illustrate the clinical, hematologic and roentgenologic features of this rare disorder.

The conspicuous clinical feature of this disease is splenomegaly which is out of proportion to the constitutional symptoms. The diagnosis is proved by the demonstration of typical Gaucher's cells in marrow aspirates. These cells may be few in number and may escape detection unless the examiner is alerted to a careful search for them.

There is no specific medical treatment for Gaucher's disease. Splenectomy may be beneficial for distressing mechanical symptoms arising from a large spleen, a hemorrhagic diathesis, or a significant hemolytic anemia.

References

1. Anderson, J. P.: Hereditary Gaucher's disease. J.A.M.A. **101**:979-981 (Sept. 23) 1933.

2. Arinkin, M.: Methodology of examining bone marrow in live patients with hematopoietic diseases. Vestnik Khir. (no. 30) **10**:57-60, 1927.

3. Oberling, C. and Woringer, P.: La Maladie de Gaucher chez la Nourrison. Rev. franc de pediat. **3**:475, 1927.

4. Reich, C., Seife, M. and Kessler, B. J.: Gaucher's disease: review and discussion of 20 cases. Medicine **30**:1-20 (Feb.) 1951.

5. Brill, N. E., Mandlebaum, F. S. and Libman, E.: Primary splenomegaly of the Gaucher type; a report of the second of four cases occurring in a single generation of one family. Am. J. M. Sc. **127**:849-859, 1909.

6. Pick, L.: Classification of diseases of lipoid metabolism and Gaucher's disease. (Dunham lecture) Am. J. M. Sc. **185**:453-469 (April) 1933.

7. Horsley, J. S., Jr., Baker, J. P., Jr., and Apperly, F. L.: Gaucher's disease of late onset with kidney involvement and huge spleen. Am. J. M. Sc. **190**:511-518 (Oct.) 1935.

8. East, T. and Savin, L. H.: Case of Gaucher's disease with biopsy of typical Pingueculae. Brit. J. Ophth. **24**:611-613 (Dec.) 1940.

9. Aballi, A. J. and Kato, K.: Gaucher's disease in early infancy; review of literature and report of case with neurological symptoms. J. Pediat. **13**:364-380 (Sept.) 1938.

10. Myers, B.: Gaucher's disease from clinical point of view. Post-Grad. M. J. **15**:20-23 (Jan.) 1939.

11. Melamed, S. and Chester, W.: Osseous form of Gaucher's disease; report of case. Arch. Int. Med. **61**:798-807 (May) 1938.

12. Squires, A. H., Kofman, O. and Cunningham, J. N.: Adult Gaucher's disease. Canad. M. A. J. **62**:178-181 (Feb.) 1950.

13. Welt, Sara, Rosenthal, Nathan and Oppenheimer, B. S.: Gaucher's splenomegaly with special reference to skeletal changes. J.A.M.A. **92**:637-643 (Feb. 23) 1929.

14. Moore, M., Jr., and Coley, B. L.: Bone lesions in Gaucher's disease. J. Tennessee M. A. **40**:101-106 (April) 1947.

15. Doan, C. A.: Hypersplenism. Bull. New York Acad. Med. **25**:625-650 (Oct.) 1949.

16. Case records of the Massachusetts General Hospital, Cabot Case 26161: Gaucher's disease with involvement of spleen, liver, adrenal glands and mesenteric lymph nodes. New England J. Med. **222**:680-684 (April 18) 1940.

17. Groen, J. and Garrer, A. H.: Adult Gaucher's disease with special reference to variations in its clinical course and value of sternal puncture as aid to its diagnosis. Blood **3**:1221-1237 (Nov.) 1948.

18. Logan, V. W.: Results of splenectomy in Gaucher's disease. Surg., Gynec. & Obst. **72**:807-814 (April) 1941.